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Multi-parametric MR imaging using apparent diffusion coefficient and fat fraction in quantification of bone marrow in pediatrics with Gaucher disease

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ABSTRACT

Purpose: To assess multi-parametric MR imaging with apparent diffusion coefficient (ADC) and fat fraction (FF) in detection and quantification of bone marrow involvement in pediatric patients with Gaucher disease.

Material and methods: This study was conducted upon 29 pediatric patients with Gaucher disease and 13 age and sex matched controls that underwent diffusion-weighted MR imaging and dual-echo gradient recalled echo imaging. The ADC and FF of the bone marrow were calculated.

Results: There was significant difference in ADC ($P = 0.001$) and FF ($P = 0.001$) of bone marrow between patients and controls. The cutoff ADC and FF differentiate patients from controls were $0.47 \times 10^{-3}\,mm^2/s$ and 0.36 with area under the curve of 0.947 and 0.885 and accuracy of 86.5% and 83.8% respectively. There was significant difference in ADC ($P = 0.001$) and FF ($P = 0.001$) between untreated ($n = 17$) and treated ($n = 12$) patients. The cutoff ADC and FF differentiate untreated from treated patients were $0.39 \times 10^{-3}\,mm^2/s$ and 0.27 with area under curve of 0.886 and 0.851 and accuracy of 88% and 84% respectively.

Conclusion: Multi-parametric MR imaging using ADC and FF are quantitative imaging parameters that can be used for detection and quantification of vertebral bone marrow involvement in pediatric patients with Gaucher disease.

1. Introduction

Gaucher disease is a metabolic disorder caused by deficiency of the lysosomal enzyme glucocerebrosidase that is characterized by the accumulation of macrophages in the bone marrow [1–2]. Gaucher disease tends to progress more rapidly in children than in adults and in approximately 50% of children growth is retarded. Early detection of bone involvement is important to arrest disease progress [3–4]. Detection of bone marrow involvement in the axial skeleton of untreated pediatric patients may indicate the need to start therapy and quantification of bone marrow involvement in treated patients is important for monitoring patients with enzyme replacement therapy [3–7]. Different MR imaging sequences are used for assessment of bone marrow involvement in patients with Gaucher disease. A variety of imaging techniques have been described including qualitative, quantitative and semi quantitative methods. Qualitative methods cannot detect degree of bone marrow involvement and semi-quantitative methods can assess disease status and response to therapy, but their results are overlapping [8–12].

Quantitative assessment of bone marrow involvement in patients with Gaucher disease is important for initial diagnosis and monitoring patients during enzyme replacement therapy [6–10]. Quantitative chemical shift imaging is a quantitative imaging parameter for detection of bone marrow involvement in Gaucher disease. Few studies have discussed the value of fat fraction (FF) in assessment of bone marrow involvement in patients with Gaucher disease [13–17]. Diffusion-weighted MR imaging provides image contrast that is dependent on the molecular motion of water, which may be substantially altered by diseases. The measured signal intensity is decreased with increased diffusivity [18–21]. Diffusion-weighted imaging with calculation of apparent diffusion coefficient (ADC) was used for assessment of bone marrow, brain and visceral organs involvement in pediatric patients with Gaucher disease [22–24].

The aim of this work is to assess multi-parametric MR imaging with ADC and FF in detection and quantification bone marrow involvement in pediatric patients with Gaucher disease.

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2. Material and method

2.1. Patients and methods

Institutional review board approval was obtained and informed consent was obtained from the parents or guardians of the children. This study included 31 consecutive pediatric patients with Gaucher disease. The inclusion criteria were patients with Gaucher disease type I proved with low glucocerebrosidase activity in leukocytes. We excluded two patients from the study due to motion artifacts with bad imaging quality. The final number of patients was 29 patients (22 boys and 7 girls, age range from 3 to 16 years; mean age 8 years) with Gaucher disease type I. The age and sex matched 13 controls (age range from 4 to 16 years; mean age 9 years) were selected from patients that underwent MR imaging for reasons other than spinal or bone marrow abnormalities. Thirteen patients were undergoing treatment with intravenous enzyme replacement therapy using imiglucerase at dose of 60 U/Kg every 2 weeks. All patients and controls underwent diffusion-weighted MR imaging and Dixon dual-echo gradient recalled echo (GRE) imaging of bone marrow of the lumbar spine. The majority of the patients in this study have previously been included in a study analyze diffusion weighted MR imaging of liver and spleen [24].

2.2. MR imaging

The MR examination of the lumbar spine was done upon T1.5 T MR unit (Ingenia, Philips medical systems, Best, Netherlands) using bipolar diffusion encoding gradient. Patients were kept fasting for 4–6 h prior to the study. Sedation was done in thirteen children with oral chloral hydrate. Diffusion-weighted MR imaging of the spine was done using a single shot spin-echo imaging in the sagittal plane. The applied parameters were TR = 3600 ms, TE = 38 ms, *b* value = 0, 500, 1000 s/mm^2, scan time was 60 s. The ADC map was reconstructed automatically. The Dixon dual-echo gradient recalled echo imaging in the sagittal section was acquired using the following parameters TR = 180 ms, TE = 2.1 ms (opposed-phase) and 4.2 ms (in-phase), slice thickness = 4 mm, flip angle = 70 degree, number of excitation = 1 and the scan time = 20 s.

2.3. Image analysis

The MR images was reviewed done by one radiologist expert in MR imaging since 25 years (AA) who was blinded to the clinical findings of the disease. A region of interest (ROI) was placed in the bone marrow of the first lumbar vertebral body away from the articular end plates at the ADC map (Fig. 1). The ADC was calculated with the following equation: The ADC was calculated according to the following formula: ADC _ $-(\ln Sb2 - \ln Sb1)/(b2 - b1)$, where ln is the natural log, and $Sb1$ and $Sb2$ are the signal intensities in the ROI placed on sections corresponding to the two different *b* values ($b1$ and $b2$) [19]. A similar ROI was placed in the in-phase and opposed-phase images for calculation of fat fraction (FF). The FF was calculated with the following equation: fat fraction (FF) = (signal intensity in-phase -signal intensity opposed-phase) / (2 X signal intensity in-phase) [14].

2.4. Statistical analysis

The statistical analysis of data was carried out using the Statistical package for social sciences version 21 [SPSS, Chicago, IL, USA]. The mean and standard deviation of ADC and FF of the bone marrow of vertebral bodies in patients and controls and treated versus untreated patients were calculated. Student's *t*-test was performed to study the difference in the ADC and FF between the two groups. The P value was considered significant if ≤ 0.05 at 95% confidence interval. A receiver operating characteristic (ROC) curve was done to calculate the cutoff value of ADC and FF used to differentiate patients from controls and treated from untreated patients with calculation of the area under the curve (AUC), sensitivity, specificity and accuracy. Pearson correlation test was used to correlate ADC with FF of the bone marrow of the lumbar spine. The correlation coefficient *r* and *P* value were calculated.

3. Results

The mean ADC of vertebral bone marrow in pediatric patients with Gaucher disease was 0.41 ± 0.06 (0.33–0.54) × 10^{-3} mm^2/s, and in control children was 0.53 ± 0.02 (0.48–0.57) × 10^{-3} mm^2/s with significant difference in between (P = 0.001). When ADC of 0.47 × 10^{-3} mm^2/s was used as a threshold parameter for differentiating children with Gaucher disease from controls, the best result was obtained with an accuracy of 86.5%, sensitivity of 80%, specificity of 100% and the area under the curve of 0.947 (Fig. 2a).

The mean ADC of the vertebral bone marrow of untreated patients (n = 16) with Gaucher disease was 0.37 ± 0.04 (0.33–0.47) × 10^{-3} mm^2/s, and of treated (n = 13) patients was 0.46 ± 0.05 (0.41–0.54) × 10^{-3} mm^2/s. There was statistically significant difference in the ADC of the vertebral bone marrow between untreated and treated patients (P = 0.001). Selection ADC of 0.39 × 10^{-3} mm^2/s as a threshold value for differentiating untreated from treated patients revealed an accuracy of 88%, sensitivity of 100%, specificity of 78.6% and area under the curve of 0.886 (Fig. 2b).

The mean FF of the vertebral bone marrow in pediatric patients with Gaucher disease was 0.29 ± 0.05 (0.21–0.42), and in controls was 0.39 ± 0.05 (0.31–0.49) with significant difference (P = 0.001). When FF of 0.36 was used as a threshold value for differentiating pediatric patients with Gaucher disease from controls, the best result was obtained with an accuracy of 83.8%, sensitivity of 88%, specificity of 75% and the area under the curve of 0.885 (Fig. 2c).

The mean FF of the vertebral bone marrow of untreated patients was 0.26 ± 0.04 (0.21–0.35), and in treated patients was 0.34 ± 0.04 (0.29–0.42). There was statistically significant difference in the FF of the vertebral bone marrow between untreated and treated patients (P = 0.001). Selection 0.27 as a threshold value of FF for differentiating untreated from treated patients revealed an accuracy of 84%, sensitivity of71.4, specificity of 71.4% and area under the curve of 0.851 (Fig. 2d).

The ADC of the vertebral bone marrow in pediatric patients with Gaucher disease was positively correlated with FF (r = 0.69, P = 0.001).

4. Discussion

The main findings in this study is ADC derived from diffusion-weighted MR imaging and FF derived from Dixon dual-echo gradient recalled echo imaging are quantitative parameter that can helps in detection and quantification of bone marrow involvement in untreated and treated pediatric patients with Gaucher disease.

Assessment of bone marrow with routine MR imaging in pediatric patients is challenging due to small volume of the bone marrow, conversion of red to fatty marrow and, different histological structure of the red marrow within pediatric age group. One of the major problems in evaluation bone marrow involvement in pediatric patients using a semiquantitative method is that it is easy to confuse hematogenous marrow signal changes with infiltrative changes in Gaucher disease due to large volume of hematogenous bone marrow in pediatric patients. This leads to false high values for the semiquantitative parameters of MR imaging [2–7]. As MR imaging has progressed we do have many more tools at our discretion to use in providing more quantitative analysis of marrow involvement in Gaucher disease.

In this study, the mean ADC of the vertebral bone marrow is lower in patients with Gaucher disease than controls. This is attributed to infiltration of lipid-overloaded macrophages Gaucher cells the bone marrow of patients with Gaucher disease. The large size, foamy cytoplasm and large multinucleated cells within Gaucher cells are

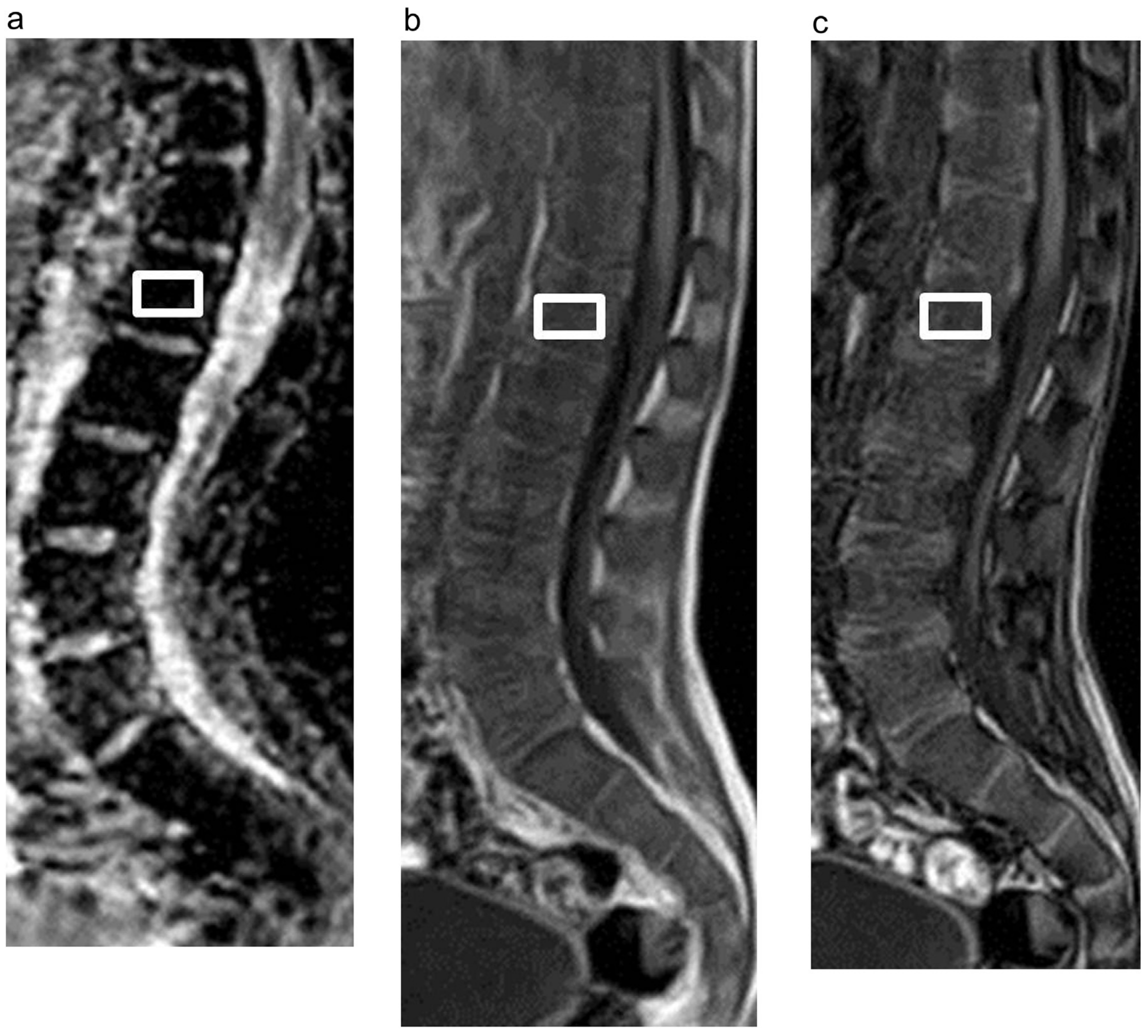

Fig. 1. Localization for region of interest at lumbar vertebral body in pediatric patient with Gaucher disease. Localization of region of interest at first lumber vertebral body at ADC map (A), in-phase image (B) and opposed-phase image (C) of the lumbar spine.

associated with restricted diffusion of the bone marrow with low ADC value [21–23]. Previous studies reported that there is negative correlation between the ADC and cellularity of bone marrow [19–20]. Another studies added that restricted diffusion with low ADC of the vertebral body, brain, and visceral organs such as liver and spleen in patients with Gaucher disease compared to controls [21–23].

In this study, the ADC can used for quantification of bone marrow in the patients with significant difference in the ADC of the bone marrow between treated and untreated patients. The ADC of the bone marrow is higher in treated patients with Gaucher disease than untreated patients. This is explained with that treatment with enzyme replacement therapy results in decreased number and degradation of Gaucher cell deposits. This changes in Gaucher cells results in decreased cellularity of the bone marrow with unrestricted diffusion and higher ADC of the bone marrow in treated patients than in untreated patients [19–23].

In this study, the FF of bone marrow in patients with Gaucher disease is lower that controls. This is attributed to Gaucher cells displaces and replaces the normal triglyceride-rich adipocytes of the bone marrow and therefore decreases the FF of the vertebral bone marrow [13–16]. The measured FF is correlated with quantitative analysis of marrow triglycerides and glucocerebrosides. Glucocerebroside concentrations are higher in Gaucher marrow and inversely correlated with triglyceride concentrations [11]. Several MR imaging sequences are used for non-invasive assessment of FF, and they are evolving. The most popular ones are the Dixon method, of which there are several versions (e.g., 2-point, 3-point, spin-echo and dual-echo gradient-recalled sequences) [13–16].

In this study, the FF can used for quantification of bone marrow in the patients with significant difference in the FF of the bone marrow between treated and untreated patients. The mean FF of the bone marrow is higher in treated patients than in untreated patients. This is attributed to treatment with enzyme replacement therapy results in decrease number of Gaucher cells and returns of normal triglyceride-rich adipocytes into the bone marrow with subsequent increase FF of the bone marrow [13–14]. Another study added that the level of FF correlate well with Gaucher disease activity [13–16].

In this study, there is correlation of the ADC derived from diffusion-weighted MR imaging of the bone marrow with the FF derived from chemical sift imaging ($r = 0.698$, $P = 0.001$). One study reported that there is correlation of the ADC of the liver and spleen with volume of liver and spleen in patients with Gaucher disease [24]. Another study added that there is correlation of FF of bone marrow in patients with Gaucher disease measured with chemical shift imaging with FF that calculated from proton MR spectroscopy [12].

Patients with Gaucher disease treated with enzyme replacement therapy that prevents accumulation of lipid within the bone marrow. Monitoring patients with Gaucher disease after enzyme replacement therapy is important as the therapy is expensive and to avoids its side effect [1–3]. Imaging can be used to track the response of patients to enzyme replacement therapy. Routine MR imaging may show changes

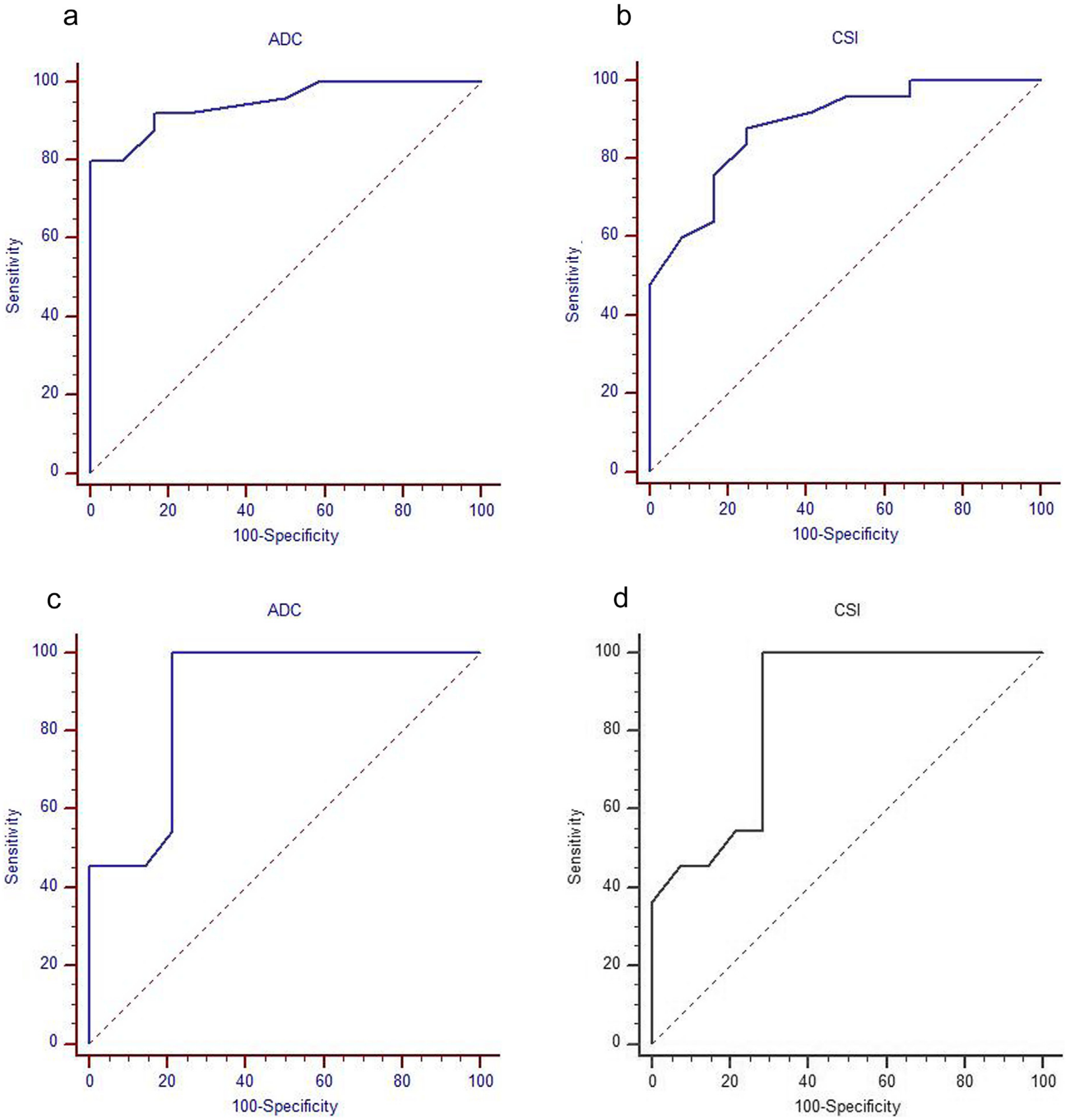

Fig. 2. Receiver Operating Characteristic Curve: (A) The threshold ADC value used to differentiate patients from controls is $0.47 \times 10^{-3}\,mm^2/s$ with an accuracy of 86.5% and the area under the curve of 0.947 ± 0.03. (B) The threshold FF used to differentiate patients from controls is 0.36 with an accuracy of 83.8% and the area under the curve of 0.885. (C) The threshold ADC value used to differentiate treated from untreated patients is $0.39 \times 10^{-3}\,mm^2/s$ with an accuracy of 88% and the area under the curve of 0.886. (D) The threshold FF used to differentiate treated from untreated patients is 0.27 with an accuracy of 84% and the area under the curve of 0.851.

in marrow signal after therapy, but, after long time of the treatment. Semi-quantitative parameters of MR imaging are used for monitoring patients with enzyme replacement therapy, but their results are overlapping [4–6]. We state that some thoughts on role of multiparametric MR imaging with ADC and FF in monitoring bone marrow response to the therapy in pediatric patients with Gaucher disease.

There are few limitations of this study. First, this study was done a 1.5 T with calculation of ADC. Further studies with using advanced MR imaging as diffusion tensor MR imaging, proton MR spectroscopy and contrast MR imaging of bone marrow upon higher 3 T scanner [25–28] will improve the results. Second, there is no correlation of ADC and FF of the bone of the vertebral body with the clinical, laboratory and genotyping of the patients with Gaucher disease. Further studies are recommended to correlates the ADC and FF of the bone marrow with genotyping and laboratory tests. Third, image analysis was performed by region of interest at L1 vertebral body. Further studies with application of advanced post processing as machine learning and histogram analysis of multiple vertebral bodies will improve the results [28–30].

5. Conclusion

We concluded that multi-parametric MR imaging using ADC and FF are quantitative imaging parameters that can be used for detection and quantification of the bone marrow involvement in pediatric patients with Gaucher disease.

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